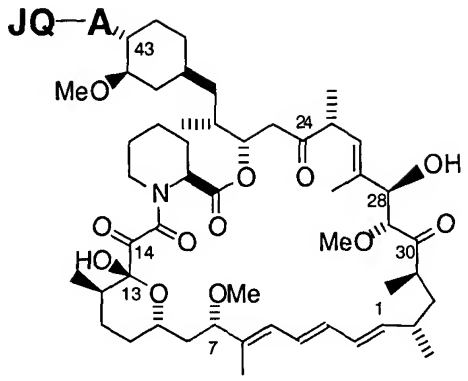
Claims

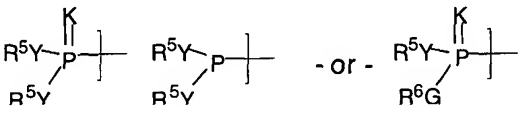
1. A compound of the formula:




and pharmaceutically acceptable derivatives thereof, wherein

A is –O–, –S– or $–NR^2–$ or is absent;

Q is absent or (if A is –O–, –S– or $–NR^2–$) Q may be –V–, –OV–, –SV–, or $–NR^2V–$, where V is an aliphatic, heteroaliphatic, aryl, or heteroaryl moiety, such that J is linked to the cyclohexyl ring directly, through A or through VA, OVA, SVA or $NR^2VA$;

J =  - or - 

K is O or S;

each occurrence of Y is independently –O–, –S–, $–NR^2–$, or a bond linking a $R^5$ moiety to P;

each occurrence of $R^2$ and $R^5$ is independently an aliphatic, heteroaliphatic, aryl, or heteroaryl moiety, or H; and

each occurrence of $R^6$ is independently $-PK(YR^5)(YR^5)$, $-SO_2(YR^5)$ or $–C(O)(YR^5)$; so long as any $R^2$ or $R^5$ moiety linked directly to P is not H;

wherein two $R^2$, $R^5$ and/or $R^6$ moieties may be chemically linked to one another to form a ring;

each occurrence of G is independently –O-, -S-, $-NR^2-$ or $(M)_x$;

each occurrence of M is independently a substituted or unsubstituted methylene moiety, and any M-M' moiety may be saturated or unsaturated;

each occurrence of x is independently an integer from 1-6;

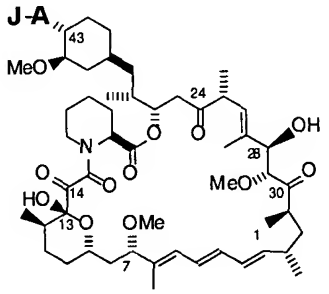
wherein each of the foregoing aliphatic and heteroaliphatic moieties is independently linear or branched, or cyclic or acyclic, and substituted or unsubstituted, and each of the aryl, heteoraryl, acyl, aroyl or heteroaroyl moieties is independently substituted or unsubstituted;

with the proviso that: J-Q-A– is not $(HO)_2(P=O)O–$; $(MeO)_2(P=O)O–$; $(R^2Y)(Me)(P=O)O–$, where $(R^2Y)$ comprises an immunogenic carrier material, detector carrier material or a solid matrix, or $(HO)_2(P=O)–W–O–$ (or a desmethyl or reduced analog of such $(HO)_2(P=O)–W–O–$containing rapamycin derivative, where W comprises a substituted or unsubstituted heterocycle comprising

alone or fused to a six-membered aromatic ring,

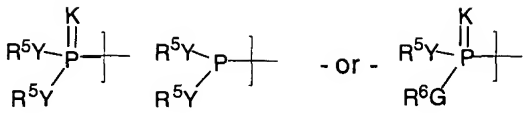
wherein U is substituted or unsubstituted amino, O, S, SO or $SO_2$; or a salt of any of the foregoing.

2. A compound of the formula:




and pharmaceutically acceptable derivatives thereof, wherein

A is –O–, –S– or $–NR^2–$ or is absent;

J =  - or - 

K is O or S;

each occurrence of Y is independently –O–, –S–, $–NR^2–$, or a bond linking a $R^5$ moiety to P;

each occurrence of $R^2$ and $R^5$ is independently an aliphatic, heteroaliphatic, aryl, or heteroaryl moiety, or H; and

each occurrence of $R^6$ is independently $-PK(YR^5)(YR^5)$, $-SO_2(YR^5)$ or $–C(O)(YR^5)$; so long as any $R^2$or $R^5$ moiety linked directly to P is not H;

wherein two $R^2$, $R^5$ and/or $R^6$ moieties may be chemically linked to one another to form a ring;

each occurrence of G is independently –O-, -S-, $-NR^2-$ or $(M)_x$;

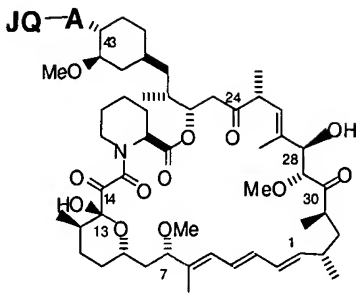
each occurrence of M is independently a substituted or unsubstituted methylene moiety, and any M-M' moiety may be saturated or unsaturated;

each occurrence of x is independently an integer from 1-6;

wherein each of the foregoing aliphatic and heteroaliphatic moieties is independently linear or branched, or cyclic or acyclic, and substituted or unsubstituted, and each of the aryl, heteroaryl, acyl, aroyl or heteroaroyl moieties is independently substituted or unsubstituted;

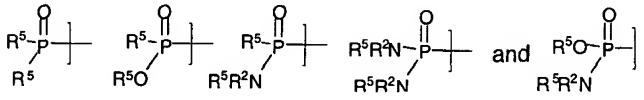
with the proviso that (a) J-A– is not $(HO)_2(P=O)O–$ or $(MeO)_2(P=O)O–$ , and (b) if JA– is $(R^2Y)(Me)(P=O)O–$, then $(R^2Y)$ is not an immunogenic carrier material, detector carrier material or a solid matrix.

3. A compound of the formula:




and pharmaceutically acceptable derivatives thereof, wherein

J is chosen from:




A is absent or is –O–, –S– or –$NR^2$–;

Q is absent or (if A is –O–, –S– or –$NR^2$–) Q may be –V–, –OV–, –SV–, or –$NR^2$V–, where V is an aliphatic, heteroaliphatic, aryl, or heteroaryl moiety, such that J is linked to the cyclohexyl ring directly, through A or through VA, OVA, SVA or $NR^2$VA;

K is O or S;

each occurrence of Y is independently –O-, -S-, –$NR^2$–, or a chemical bond linking a $R^5$ moiety to P;

each occurrence of $R^2$ and $R^5$ is independently an aliphatic, heteroaliphatic, aryl, or heteroaryl moiety, or H; and each occurrence of $R^6$ is independently -$PK(YR^5)(YR^5)$, -$SO_2(YR^5)$ or –$C(O)(YR^5)$; so long as any $R^2$ or $R^5$ moiety linked directly to P is not H;

wherein two $R^2$, $R^5$ and/or $R^6$ moieties may be chemically linked to one another to form a ring;
each occurrence of G is independently –O-, -S-, -$NR^2$- or $(M)_X$;

each occurrence of M is independently a substituted or unsubstituted methylene moiety, and any M-M' moiety may be saturated or unsaturated;

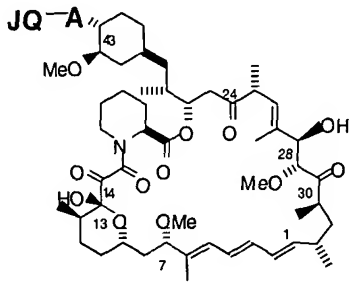
each occurrence of x is independently an integer from 1-6;

wherein each of the foregoing aliphatic and heteroaliphatic moieties is independently linear or branched, or cyclic or acyclic, and substituted or unsubstituted, and each of the aryl, heteroaryl, acyl, aroyl or heteroaroyl moieties is independently substituted or unsubstituted;

in which each occurrence of $R^2$ and $R^5$ is an independently chosen lower aliphatic or aryl moiety, which may be substituted or unsubstituted, except that in addition, $-OR^5$ and $-NR^2R^5$, may be –OH and $-NHR^5$;

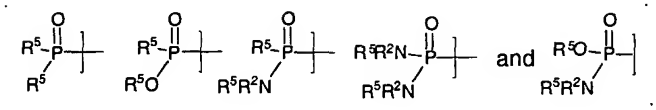
with the proviso that if J-Q-A– is $(R^2Y)(Me)(P=O)O-$, then $(R^2Y)$ is not an immunogenic carrier material, detector carrier material or a solid matrix, or a salt thereof.

4. A compound of the formula:




and pharmaceutically acceptable derivatives thereof, wherein

J is chosen from:




A is absent or is –O–, –S– or $-NR^2-$;

Q is absent or (if A is –O–, –S– or $–NR^2–$) Q may be –V–, –OV–, –SV–, or $–NR^2V–$, where V is an aliphatic, heteroaliphatic, aryl, or heteroaryl moiety, such that J is linked to the cyclohexyl ring directly, through A or through VA, OVA, SVA or $NR^2VA$;

K is O or S;

each occurrence of Y is independently –O-, -S-, $–NR^2–$, or a chemical bond linking a $R^5$ moiety to P;

in which each occurrence of $R^2$ and $R^5$ is an independently chosen lower aliphatic or aryl moiety, which may be substituted or unsubstituted, except that in addition, $–OR^5$ and $–NR^2R^5$, may be –OH and $–NHR^5$;

each occurrence of $R^6$ is independently $-PK(YR^5)(YR^5)$, $-SO_2(YR^5)$ or $–C(O)(YR^5)$; so long as any $R^2$, or $R^5$ moiety linked directly to P is not H;

wherein two $R^2$, $R^5$ and/or $R^6$ moieties may be chemically linked to one another to form a ring;

wherein each of the foregoing aliphatic and heteroaliphatic moieties is independently linear or branched, or cyclic or acyclic, and substituted or unsubstituted, and each of the aryl, heteoraryl, acyl, aroyl or heteroaroyl moieties is independently substituted or unsubstituted;

with the proviso that if J-Q-A– is $(R^2Y)(Me)(P=O)O–$, then $(R^2Y)$ contains 15 or fewer carbon atoms.

5. The compound of claim 1 in which each occurrence of $R^2$ and $R^5$ is an independently chosen C1 – C6 alkyl group optionally bearing one or more halo, –OH, alkoxyl–, alkyloxyalkyloxy–, haloalkyl–, hydroxyalkoxyl–, hetrocyclic, aryl or heteroaryl substituents, except that in addition, $–OR^5$ and $–NR^2R^5$, may be –OH and $–NHR^5$.

6. The compound of claim 2 in which each occurrence of $R^2$ and $R^5$ is an independently chosen C1 – C6 alkyl group optionally bearing one or more halo, –OH, alkoxyl–, alkyloxyalkyloxy–, haloalkyl–, hydroxyalkoxyl–, hetrocyclic, aryl or heteroaryl substituents, except that in addition, $–OR^5$ and $–NR^2R^5$, may be –OH and $–NHR^5$.

7. The compound of claim 3 in which each occurrence of $R^2$ and $R^5$ is an independently chosen C1 – C6 alkyl group optionally bearing one or more halo, –OH, alkoxyl–, alkyloxyalkyloxy–, haloalkyl–, hydroxyalkoxyl–, hetrocyclic, aryl or heteroaryl substituents, except that in addition, $–OR^5$ and $–NR^2R^5$, may be –OH and $–NHR^5$.

8. The compound of claim 4 in which each occurrence of $R^2$ and $R^5$ is an independently chosen C1 – C6 alkyl group optionally bearing one or more halo, –OH, alkoxyl–, alkyloxyalkyloxy–, haloalkyl–, hydroxyalkoxyl–, hetrocyclic, aryl or heteroaryl substituents, except that in addition, $–OR^5$ and $–NR^2R^5$, may be –OH and $–NHR^5$.

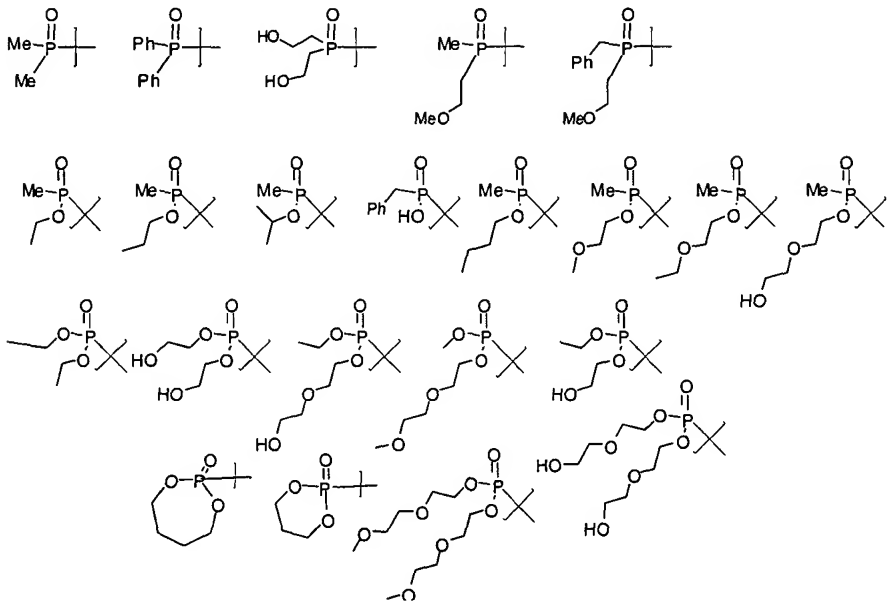
9. The compound of claim 5 in which each occurrence of $R^2$ and $R^5$ is independently chosen from methyl, ethyl, n-propyl, --propyl, n-butyl, 2-butyl, t-butyl, phenyl, or heteroaryl, each of which optionally bearing one or more halo, –OH, alkoxyl–, alkoxylalkoxyl–, haloalkyl–, hydroxyalkoxyl–, heterocyclic, aryl or heteroaryl substituents, and in addition, $–OR^5$ and $–NR^2R^5$, may be –OH and $–NHR^5$.

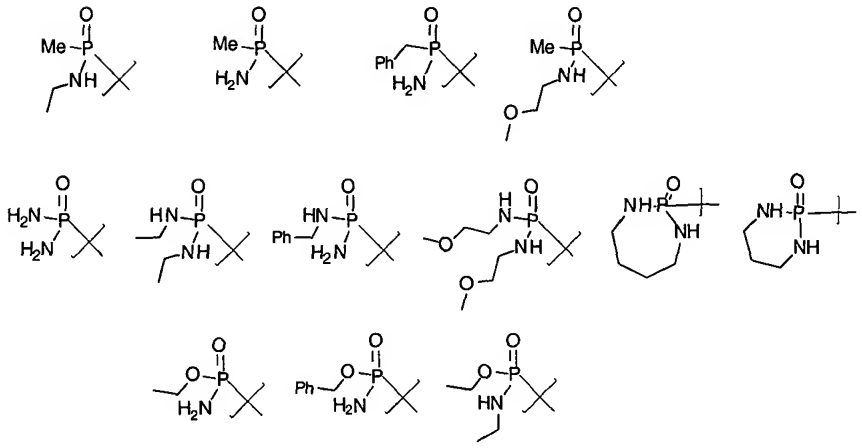
10. The compound of claim 6 in which each occurrence of $R^2$ and $R^5$ is independently chosen from methyl, ethyl, n-propyl, --propyl, n-butyl, 2-butyl, t-butyl, phenyl, or heteroaryl, each of which optionally bearing one or more halo, –OH, alkoxyl–, alkoxylalkoxyl–, haloalkyl–, hydroxyalkoxyl–, heterocyclic, aryl or heteroaryl substituents, and in addition, $–OR^5$ and $–NR^2R^5$, may be –OH and $–NHR^5$.

11. The compound of claim 7 in which each occurrence of $R^2$ and $R^5$ is independently chosen from methyl, ethyl, n-propyl, --propyl, n-butyl, 2-butyl, t-butyl, phenyl, or heteroaryl, each of which optionally bearing one or more halo, –OH, alkoxyl–, alkoxylalkoxyl–, haloalkyl–, hydroxyalkoxyl–, heterocyclic, aryl or heteroaryl substituents, and in addition, $–OR^5$ and $–NR^2R^5$, may be –OH and $–NHR^5$.

12. The compound of claim 8 in which each occurrence of $R^2$ and $R^5$ is independently chosen from methyl, ethyl, n-propyl, --propyl, n-butyl, 2-butyl, t-butyl, phenyl, or heteroaryl, each of which optionally bearing one or more halo, –OH, alkoxyl–, alkoxylalkoxyl–, haloalkyl–, hydroxyalkoxyl–, heterocyclic, aryl or heteroaryl substituents, and in addition, $–OR^5$ and $–NR^2R^5$, may be –OH and $–NHR^5$.

13. The compound of claim 1 wherein J is chosen from the following:





14. The compound of claim 1 in which QA is –O–, –OVO–, –NH–, –OVNH–, –S–, or –SVS–, where V is a lower aliphatic moiety.

15. The compound of claim 4 in which QA is –O–, –OVO–, –NH–, –OVNH–, –S–, or –SVS–, where V is a lower aliphatic moiety.

16. The compound of claim 5 in which QA is –O–, –OVO–, –NH–, –OVNH–, –S–, or –SVS–, where V is a lower aliphatic moiety.

17. The compound of claim 8 in which QA is –O–, –OVO–, –NH–, –OVNH–, –S–, or –SVS–, where V is a lower aliphatic moiety.

18. The compound of claim 9 in which QA is –O–, –OVO–, –NH–, –OVNH–, –S–, or –SVS–, where V is a lower aliphatic moiety.

19. The compound of claim 13 which comprises a moiety JQA– in which QA is –O–, –OVO–, –NH–, –OVNH–, –S–, or –SVS–, where V is a lower aliphatic moiety.

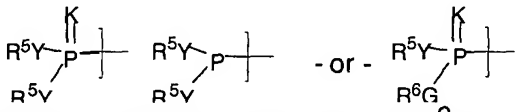
20. The compound of any of claims 1 – 19 in which JQA– or JA– comprises $(R^2Y)(Me)(P=O)O–$ in which $R^2Y–$ contains 15 or fewer carbon atoms.

21. The compound of claim 20 in which JQA– comprises $(R^2Y)(Me)(P=O)O–$ in which $R^2Y–$ contains 10 or fewer carbon atoms.

22. A compound comprising a derivative of rapamycin or 43-epi-rapamycin in which the hydroxyl group at position 43 is replaced by a group JQA–, wherein:

A is –O–, –S– or $–NR^2–$ or is absent;

Q is absent or (if A is –O–, –S– or $–NR^2–$) Q may be –V–, –OV–, –SV–, or $–NR^2V–$, where V is an aliphatic, heteroaliphatic, aryl, or heteroaryl moiety, such that J is linked to the cyclohexyl ring directly,

J =  - or - 

through A or through VA, OVA, SVA or $NR^2VA$;

K is O or S;

each occurrence of Y is independently –O–, –S–, $–NR^2–$, or a bond linking a $R^5$ moiety to P;

each occurrence of $R^2$ and $R^5$ is independently an aliphatic, heteroaliphatic, aryl, or heteroaryl moiety, or H; and each occurrence of $R^6$ is independently $-PK(YR^5)(YR^5)$, $-SO_2(YR^5)$ or $-C(O)(YR^5)$; so long as any $R^2$ or $R^5$ moiety linked directly to P is not H; wherein two $R^2$, $R^5$ and/or $R^6$ moieties may be chemically linked to one another to form a ring;

each occurrence of G is independently –O-, -S-, $-NR^2-$ or $(M)_x$;

each occurrence of M is independently a substituted or unsubstituted methylene moiety, and any M-M' moiety may be saturated or unsaturated;

each occurrence of x is independently an integer from 1-6;

wherein each of the foregoing aliphatic and heteroaliphatic moieties is independently linear or branched, or cyclic or acyclic, and substituted or unsubstituted, and each of the aryl, heteroaryl, acyl, aroyl or heteroaroyl moieties is independently substituted or unsubstituted;

with one or more of the following additional features:

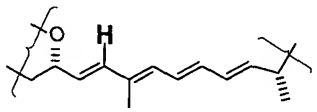
(a) epimerization at position 28, or replacement of the position 28 hydroxyl group (in either sterochemical orientation) with halo, $-OR^2$ or $-OC(=O)AR^2$;

(b) replacement of the ketone at position 24 with a substituted or unsubstituted oxime, or with a hydroxyl group or derivative thereof of the formula $-OR^2$ or $-OC(=O)AR^2$;

(c) replacement of the ketone at position 24 with a substituted or unsubstituted oxime, or with a hydroxyl group or derivative thereof of the formula $-OR^2$ or $-OC(=O)AR^2$;

(d) epimerization of the –OMe at position 7 and/or replacement of the –OMe with a moiety selected from H, halo, $-R^A$, $-OR^A$, $-SR^A$, $-OC(O)R^A$, $-OC(O)NR^AR^B$, $-NR^AR^B$, $-NR^BC(O)R^A$, $-NR^BC(O)OR^A$, $-NR^BSO2R^A$ or $-NR^BSO2NR^AR^{B'}$; where $R^A$ is $R^2$ and where $R^B$ is OH or $R^2$; and

(e) elimination of the –OMe at position 7 yielding the tetra-ene moiety:

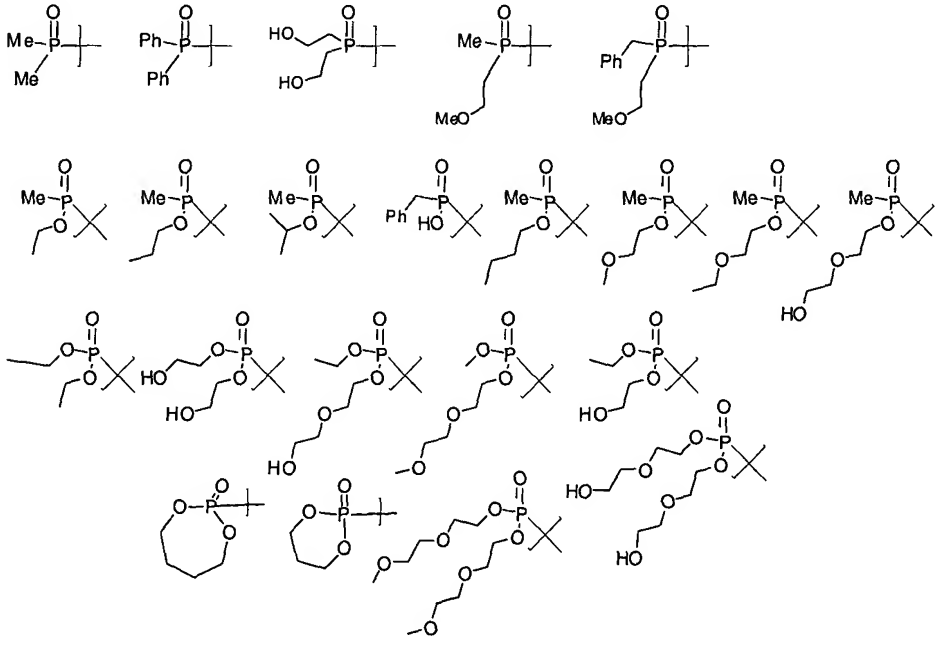


23. The compound of claim 22 in which each occurrence of $R^2$ and $R^5$ is an independently chosen C1 – C6 alkyl group optionally bearing one or more halo, –OH, alkoxyl–, alkyloxyalkyloxy–, haloalkyl–, hydroxyalkoxyl–, hetrocyclic, aryl or heteroaryl substituents, except that in addition, $-OR^5$ and $-NR^2R^5$, may be –OH and $-NHR^5$.

24. The compound of claim 23 in which each occurrence of $R^2$ and $R^5$ is independently chosen from methyl, ethyl, n-propyl, --propyl, n-butyl, 2-butyl, t-butyl, phenyl, or heteroaryl, each of which optionally bearing one or more halo, –OH, alkoxyl–, alkoxylalkoxyl–, haloalkyl–, hydroxyalkoxyl–, heterocyclic, aryl or heteroaryl substituents, and in addition, $-OR^5$ and $-NR^2R^5$, may be –OH and $-NHR^5$.

25. The compound of claim 22 in which QA is –OVO–, –OVNH– or –SVS–, where V is a lower aliphatic moiety.

26. The compound of any of claims 22 - 25 wherein J is chosen from the following:



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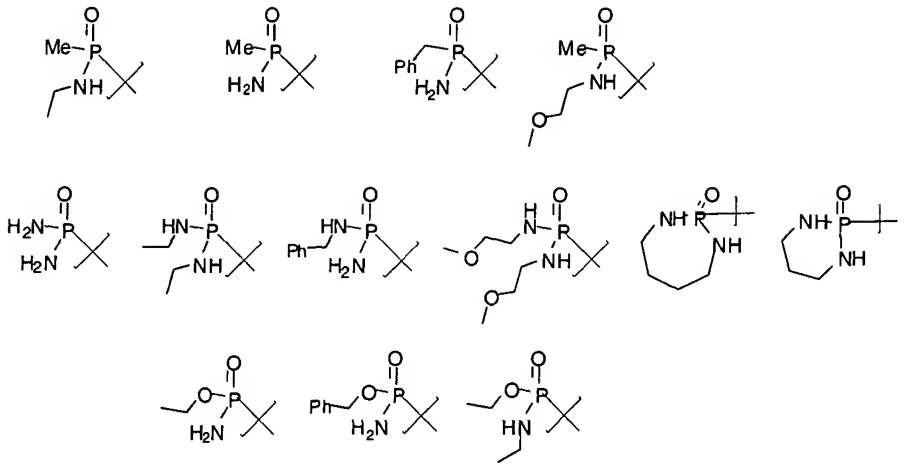

27. A composition comprising (a) a compound of any of claims 1 through 19 or 22 through 25, and (b) a pharmaceutically acceptable vehicle, optionally containing (c) one or more pharmaceutically acceptable excipients.

28. A composition suitable for oral administration to a mammal, the composition comprising (a) a compound of any of claims 1 through 19 or 22 through 25, and (b) a pharmaceutically acceptable vehicle, optionally containing (c) one or more pharmaceutically acceptable excipients.

29. A composition suitable for parenteral administration to a mammal, the composition comprising (a) a compound of any of claims 1 through 19 or 22 through 25, and (b) a pharmaceutically acceptable vehicle, optionally containing (c) one or more pharmaceutically acceptable excipients.

30. A method for suppressing the immune response of a subject by administering to the subject an immunosuppressive amount of a composition of claim 27.

31. A method for treating or suppressing the rejection of transplanted tissues in a recipient, which method comprises administering to said recipient an effective amount of a composition of claim 27.

32. A method for treating graft vs. host disease, lupus, rheumatoid arthritis, diabetes mellitus, myasthenia gravis, multiple sclerosis, psoriasis, dermatitis, eczema, seborrhea, inflammatory bowel disease, pulmonary inflammation, ocular uveitis; adult T-cell leukemia/lymphoma; fungal infections; hyperproliferative restenosis; graft vascular atherosclerosis; cerebral vascular disease, coronary artery disease, cerebrovascular disease, arteriosclerosis, atherosclerosis, nonatheromatous arteriosclerosis, or

vascular wall damage from cellular events leading toward immune mediated vascular damage, stroke or multiinfarct dementia in a subject in need thereof, which method comprises administering to said subject a therapeutically effective amount of a composition of claim 27.

33. A method for treating coronary artery disease, cerebrovascular disease, arteriosclerosis, atherosclerosis, nonatheromatous arteriosclerosis, vascular wall damage from cellular events leading toward immune mediated vascular damage, stroke or multiinfarct dementia in a subject in need thereof, the method comprising administering to the subject a composition of claim 27 in combination with an ACE inhibitor (such as quinapril, perindopril, ramipril, captopril, trandolapril, fosinopril, lisinopril, moexipril, and enalapril); angiotensin II receptor antagonist (such as candesartan, irbesartan, losartan, valsartan, and telmisartan); fibric acid derivative (such as clofibrate, and gemfibrozil); HMG Co-A reductase inhibitor (such as cerivastatin, fluvastatin, atorvastatin, lovastatin, pravastatin, or simvastatin); beta adrenergic blocking agent (such as sotalol, timolol, esmolol, carteolol, propranolol, betaxolol, penbutolol, nadolol, acebutolol, atenolol, metoprolol, and bisoprolol); calcium channel blocker (such as nifedipine, verapamil, nicardipine, diltiazem, nimodipine, amlodipine, felodipine, nisoldipine, and bepridil); antioxidant; anticoagulant (such as warfarin, dalteparin, heparin, enoxaparin, and danaparoid); or agent useful in hormone replacement therapy containing estrogens (such as conjugated estrogens, ethinyl estradiol, 17-beta-estradiol, estradiol, and estropipate).

34. A method for treating cancer in a subject in need thereof, which comprises administering to the subject a treatment effective amount of a composition of claim 27.

35. The method of claim 34 wherein the treatment is provided in combination with one or more other cancer therapies.

36. The method of claim 35 wherein the other therapy or therapies comprise the administration to the subject of one or more of an anti-cancer alkylating or intercalating agent; an antiestrogen; an inhibitor of a kinase (e.g., Src, BRC/Abl, kdr, aurora-2, glycogen synthase kinase 3 ("GSK-3")); an antibody to a receptor or hormone implicated in a cancer (e.g. EGFR, PDGFR, IGF-R and IL-2);, or a soluble receptor or other receptor antagonist to such receptor; a proteasome inhibitor or other NF-kB inhibitor; or radiation.

37. The method of claim 35 wherein the other therapy or therapies comprise the administration to the subject of one or more of Zyloprim, alemtuzmab, altretamine, amifostine, nastrozole, antibodies against prostate-specific membrane antigen (such as MLN-591, MLN591RL and MLN2704), arsenic trioxide, Avastin ® (or other anti-VEGF antibody), bexarotene, bleomycin, busulfan, capecitabine, carboplatin, Gliadel Wafer, celecoxib, chlorambucil, cisplatin, cisplatin-epinephrine gel, cladribine, cytarabine liposomal, daunorubicin liposomal, daunorubicin, daunomycin, dexrazoxane, docetaxel, doxorubicin,

Elliott's B Solution, epirubicin, estramustine, etoposide phosphate, etoposide, exemestane, fludarabine, 5-FU, fulvestrant, gemcitabine, gemtuzumab-ozogamicin, goserelin acetate, hydroxyurea, idarubicin, idarubicin, Idamycin, ifosfamide, imatinib mesylate, irinotecan (or other topoisomerase inhibitor, including antibodies such as MLN576 (XR11576)), letrozole, leucovorin, leucovorin levamisole,liposomal daunorubicin, melphalan, L-PAM, mesna, methotrexate, methoxsalen, mitomycin C, mitoxantrone, MLN518 or MLN608 (or other inhibitors of the flt-3 receptor tyrosine kinase, PDFG-R or c-kit), itoxantrone, paclitaxel, Pegademase, pentostatin, porfimer sodium, Rituximab (RITUXAN®), talc, tamoxifen, temozolamide , teniposide, VM-26 , topotecan, toremifene, Trastuzumab (Herceptin®, or other anti-Her2 antibody), 2C4 (or other antibody which interferes with HER2-mediated signaling), tretinoin, ATRA, valrubicin, vinorelbine, or pamidronate, zoledronate or another bisphosphonate.

38. A drug eluting vascular stent comprising a vascular stent containing a compound of any of claims 1 through 19 or 22 through 25, dispersed in a matrix or disposed in channels, reservoirs or other chambers on or in said stent.

39. A drug eluting stent of claim 38 wherein the stent is an Angiomed (Bard) , Cardiocoil (In-Stent Medtronic), CORINTHIAN (BSC), Radius (Scimed), Wallstent (Schneider), Act-one (ACT), Angiostent (angioynamics), be-Stent (In-Stent Medtronic), BiodivYsio (Biocompatibles), Cordiś, Cross-flex (Cordis), Crown (JJIS), Freedom (Global therapeutics), Gianturco-Roubin II (Cook), Jo-med, Jostent flex (Jomed), Microstent GFX (AVE), Multilink (Guidant-ACS), NIR (Medinol), NIR Royal (Medinol), NIRflex (Medinol),, NIRSIDE flex (Medinol), Palmaz-Scatz (JJIS), STS (De Scheerder), Tensum (Biotronic), Wiktor-GX (Medtronic), Wiktor-I (Medtronic), X-Trode (Bard), Y-Flex (Devon), Tsunami (Terumo), Bx Velocity (J&J), SLK-View (Advanced Stent Technologies, Inc.) or Duraflex (Avantec) stent.